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Insulin Like Growth Factor-I: A Critical Mediator of the Skeletal Response to Parathyroid Hormone

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Abstract

This review focuses on the mechanisms by which PTH stimulates both osteoblast and osteoclast function, emphasizing the critical role that IGF-I plays in these processes. After reviewing the current literature on the skeletal actions of PTH and the modulation of IGF action on bone by the different IGF-binding proteins, the review then examines studies from mouse models in which IGF-I or its receptor have been selectively deleted in different cells of the skeletal system, in particular osteoprogenitors, mature osteoblasts, and osteoclasts. Mice in which IGF-I production has been deleted from all cells are deficient in both bone formation and bone resorption with few osteoblasts or osteoclasts in bone *in vivo*, reduced osteoblast colony forming units, and an inability of either the osteoblasts or osteoclast precursors to support osteoclastogenesis *in vitro*. Mice in which the IGF-I receptor is specifically deleted in mature osteoblasts have a mineralization defect *in vivo*, and bone marrow stromal cells from these mice fail to mineralize *in vitro*. Mice in which the IGF-I receptor is deleted in osteoprogenitor cells have a marked reduction in osteoblast proliferation and differentiation leading to osteopenia. Finally mice lacking the IGF-I receptor in their osteoclasts have increased bone and decreased osteoclast formation. PTH fails to stimulate bone formation in the mice lacking IGF-I or its receptor in osteoblasts or enhance the signaling between osteoblasts and osteoclasts through RANKL/RANK and Ephrin B2/Eph B4, emphasizing the role IGF-I signaling plays in cell-communication per se and as stimulated by PTH.

Keywords

Insulin like growth factor; osteoblasts; osteoclasts; osteoprogenitors; parathyroid hormone

PARATHYROID HORMONE/IGF INTERACTIONS: AN OVERVIEW AND INTRODUCTION TO A WORKING MODEL

Parathyroid hormone (PTH) stimulates both bone formation and resorption, the balance of which is dependent on the pharmacodynamics of administration. When given intermittently PTH is anabolic for most skeletal sites [1–3]. This has led to approval of PTH for the treatment of osteoporosis. Continuous exposure to PTH is catabolic as its stimulation of bone resorption exceeds that of bone formation [4, 5]. PTH is thought to stimulate bone resorption primarily by induction of receptor activator of NF- κ B ligand (RANKL) and

suppression of osteoprotegerin (OPG) by osteoblasts resulting in the differentiation and subsequent activation of osteoclast precursors [4]. These effects *in vivo* can be reproduced *in vitro*. The mature osteoblast appears to be an important target for these actions of PTH in that the receptor for PTH (PTH-R) increases with differentiation (maturation) of the osteoblast, and the ability of PTH to induce RANKL and osteoclastogenesis parallels PTH-R expression [6]. Thus the effects of PTH on osteoclastogenesis appear to be mediated by its action on osteoblasts.

The mechanism by which PTH stimulates bone formation remains less well understood. PTH administration *in vivo* increases osteoblast number *in vivo* and osteoprogenitor number and their subsequent differentiation *in vitro* [7, 8]. One possibility is that early osteoprogenitors are directly stimulated by PTH to proliferate and differentiate. We have recently shown that PTH *in vitro* can acutely (within minutes) increase markers of proliferation and differentiation, but such changes are transient, and if PTH exposure is prolonged inhibition of proliferation and differentiation results [9]. On the other hand stimulation of osteoprogenitor proliferation and differentiation by PTH may require signals from other cells. As noted above, we have observed that the PTH-R levels increase with osteoblast maturation, suggesting that mature osteoblasts may be the target for PTH, which in turn elaborate paracrine factors such as insulin like growth factor-I (IGF-I) that act on the osteoprogenitors [7]. Furthermore, inhibition of osteoclastogenesis (c-fos null mouse) or osteoclast function (bisphosphonate treatment) blocks the ability of PTH to stimulate bone formation implicating osteoclasts or their precursors in the anabolic actions of PTH [10]. The role of the osteoclast in osteoprogenitor proliferation/differentiation may involve direct cell-cell interactions (*e.g. via* ephrinB2/EphB4 signaling) [11] or the elaboration of paracrine signals such as IGF-I from the osteoclast to the osteoblast [12].

We propose that IGF-I, a growth factor induced by PTH in osteoblasts, is required for the anabolic and catabolic actions of PTH on bone. This proposal comes from our studies with various animal models in which IGF-I and its receptor have been deleted in specific cell types in the skeleton. IGF-I stimulates osteoprogenitor proliferation and differentiation [13] as well as osteoclast formation *in vitro* [14]. Mice in which IGF-I production has been deleted from all cells (IGF-IKO) are deficient in both bone formation and bone resorption with few osteoblasts or osteoclasts in bone *in vivo*, reduced osteoblast colony forming units, and an inability of either the osteoblasts or osteoclast precursors to support osteoclastogenesis *in vitro* [14, 15]. Mice in which the IGF-I receptor is specifically deleted in mature osteoblasts (IGF-I_{Rob}KO) have a mineralization defect *in vivo* [16], and bone marrow stromal cells (BMSC) from IGF-I_{Rob}KO fail to mineralize *in vitro* [7]. When the IGF-IR is deleted in osteoprogenitors (IGF-I_{Op}KO), a reduction in osteoblast number and proliferation is observed in addition to decreased osteoblast differentiation and mineralization [17]. Mice lacking the IGF-IR in osteoclast precursors (IGF-I_{Roc}KO) have increased bone and decreased osteoclastogenesis [18]. PTH fails to stimulate bone formation in the IGF-IKO or IGF-I_{Rob}KO. Of particular interest is the observation that the IGF-IR in the mature osteoblast is required for the ability of PTH *in vivo* to stimulate osteoprogenitor cell proliferation and differentiation measured *in vitro* [7] indicating a clear requirement for signaling from the mature osteoblast to the osteoprogenitor to mediate this action of PTH.

Our working model proposes that PTH stimulates IGF-I production by the osteoblast, and the IGF-I so produced promotes the proliferation and differentiation of osteoprogenitors as well as facilitating the ability of the mature osteoblast to terminally differentiate and promote osteoclastogenesis (Fig. 1). IGF-I plays a paracrine role to stimulate osteoprogenitor proliferation and differentiation. Similarly, IGF-I, RANKL, and m-CSF elaborated by the mature osteoblast under PTH stimulation promote osteoclastogenesis, which in turn facilitates osteoprogenitor proliferation and differentiation perhaps also by

releasing IGF-I and/or *via* the bidirectional signaling of ephrinB2/EphB4. At this stage we favor the mature osteoblast as the major site for PTH regulation of these events but cannot exclude the alternative and not mutually exclusive possibility that PTH has its major impact on osteoprogenitors, and may also directly act on osteoclast precursors. This brief review will provide the evidence for implicating IGF-I in the anabolic and catabolic actions of PTH.

SKELETAL RESPONSE TO PTH

Intermittent administration of PTH has proven a remarkably effective therapy for osteoporosis. It increases bone mineral density at the hip and spine and reduces fractures [1–3]. However, PTH is a two edged sword in that continuous administration increases bone resorption more than formation (continuous PTH administration may actually decrease bone formation in some models) [4, 5] resulting in bone loss. The catabolic actions may also apply in normal physiology in that hypoparathyroid subjects (humans and mice) have increased bone mass relative to normal or hyperparathyroid subjects [19, 20]. Both gender and region of bone examined can influence the results [21–24]. Studies in rodents consistently show a positive anabolic action of intermittent PTH on both cancellous and cortical bone [25], although regional differences are still apparent [26, 27]. The developmental stage of the animal also makes a difference. The PTH null mouse at birth shows decreased cartilage matrix mineralization, decreased neovascular invasion with decreased expression of angiopoietin-1, decreased trabecular bone volume (proximal tibia), and decreased numbers of osteoblasts and osteoclasts [28]. However, these defects resolve postnatally such that by 2mo of age no apparent growth plate abnormalities can be seen, and both trabecular and cortical bone are increased over wildtype controls, although bone formation and osteoclast number are still reduced [20]. In contrast, PTHrP null mice die shortly after birth with gross distortion of the hypertrophic zone and decreased chondrocyte proliferation [29]. We have observed that the global deletion of IGF-I [15] or the chondrocyte specific deletion of IGF-IR [30] resembles the more severe phenotype of the PTHrP null mouse, whereas the deletion of IGF-IR in osteoblasts [7, 16] more closely resembles that of the PTH null mouse, providing initial evidence that lack of IGF-I signaling may impair responsiveness to PTHrP in cartilage and PTH in bone.

The site specific target cells for PTH are not totally defined. Rouleau *et al.* [31] identified a spindly shaped cell in the intertrabecular region of the metaphysis which accounted for the majority of binding to radiolabelled PTH infused into the animal. Subsequent studies including our own using immunolocalization and in situ hybridization have localized the PTH receptor (PTH-R) in chondrocytes and osteoblasts of the primary and secondary spongiosa [13, 32, 33]. Spindle shaped mononuclear cells located between blood vessels and osteoblasts, osteocytes, and flat lining cells have also been shown to have the PTH-R [33, 34]. In cultures of primary mouse osteoblasts, we [6] have observed that the expression of the PTH-R increases as the bone cells differentiate, suggesting that PTH-R is found in highest levels in the mature osteoblast. However, this does not exclude their existence in less differentiated osteoblasts or even stem and myeloid precursor cells.

The mechanism by which PTH stimulates bone formation is unclear. PTH, given intermittently, stimulates bone formation more than bone resorption, an effect associated with a rapid increase in the mRNA levels for runx2, osteocalcin, alkaline phosphatase, and collagen 1 [26, 35]. When bone marrow stromal cells (BMSC) are evaluated *in vitro*, more colony forming units and an increased percentage of alkaline phosphatase positive colonies are observed when the cells are taken from animals treated *in vivo* with PTH [7, 26], suggesting that PTH promotes the proliferation and/or differentiation of osteoblast precursors, in addition to stimulating the function of the mature osteoblast, although increased survival of osteoblasts may also contribute [36]. We and others have shown that

PTH administration to bone cells *in vitro* results in rapid and transient increases and/or activation of transcription factors associated with proliferation and differentiation such as c-fos, c-jun, c-myc, CREB, and runx2 [8, 32, 37, 38], and directly stimulates proliferation and differentiation when administered transiently [9, 39–41]. These data support an effect of PTH on both the osteoprogenitor and the mature osteoblast. Prolonged exposure was inhibitory [6, 9, 13, 41].

Several studies suggest that osteoclasts or osteoclast precursors are required for these anabolic actions of PTH. Clinical studies have demonstrated that bisphosphonates, which inhibit osteoclast function and promote their apoptosis, block much of the increase in BMD following PTH treatment [2, 3]. c-fos null mice (which lack functional osteoclasts) fail to respond to PTH [10]. However, other studies in which osteoclast numbers and/or function were inhibited with either alendronate or osteoprotegerin (OPG) did not show marked suppression of the anabolic actions of PTH [42]. Recently it has been shown that osteoclasts expressing ephrinB2 can stimulate early osteoblast differentiation *via* the ephrinB2 receptor EphB4 in osteoblasts, supporting the concept of a role for osteoclast/osteoblast interactions that could promote osteoblast proliferation and differentiation [11]. Of interest is that this ephrinB2:EphB4 interaction results in a decrease in osteoclastogenesis (unlike RANKL:RANK interaction) providing a potential mechanism by which PTH can increase anabolism over catabolism if it were to promote the ephrinB2:EphB4 interaction. We [12] have shown that PTH stimulates transcription of ephrinB2 and EphB4 in bone and bone marrow stromal cells (BMSC), an action blocked by deletion of the IGF-IR in osteoblasts [17]. Similar results with respect to PTH stimulation of ephrin B2 have recently been reported by Allan *et al.* [43].

PTH rapidly stimulates RANKL *in vivo* and *in vitro* and stimulates the ability of mature osteoblasts to promote osteoclastogenesis [4, 6, 27, 44]. Of particular interest is that PTH acutely increases OPG expression as well, but prolonged exposure (24 hr) inhibits OPG expression but not RANKL expression [4, 6, 44]. Thus the differential effect of short vs prolonged exposure to PTH on osteoblast proliferation and differentiation relative to the promotion of osteoclastogenesis may underlie the differential effect of short vs prolonged exposure to PTH with respect to the balance of its anabolic and catabolic actions. In either case PTH requires the IGF-I signaling pathway to be fully effective.

PTH stimulates a number of signaling pathways in bone cells including PKA and PKC activation, which can lead to activation of transcription factors such as runx2, members of the AP-1 family such as c-fos and c-jun, CREB, and C/EBP δ [38, 45]. However, most studies indicate that PKA activation is sufficient for most if not all of the anabolic actions of PTH [36, 46]. A C/EBP δ response element is found in the untranslated region of the first exon of the IGF-I gene, and provides the mechanism by which PTH (and other activators of PKA) induce IGF-I production. More recently the wnt signaling pathway has been implicated with the demonstration that PTH inhibits Dkk1 [47, 48] and SOST [49] expression (the products of which are inhibitors of wnt signaling acting at the level of LRP5/6) in a manner also linked to PKA activation [47]. However, PTH has been shown to activate wnt signaling in mice overexpressing Dkk1 [48] and retains its anabolic effects on bone in mice null for LRP5 [50, 51] indicating that at least the initial stages of canonical wnt signaling pathway may not be critical for the anabolic actions of PTH. In this regard PTH has recently been shown to stimulate the phosphorylation of and so inactivate GSK3 β in a manner blocked by the PKA inhibitor H89 but not by Dkk1, consistent with a downstream regulation of wnt signaling [48].

Although stimulation of the wnt signaling pathway is an attractive model to explain PTH action, our investigations have focused on the IGF-I signaling pathway. The observations

that PTH stimulates IGF-I production by osteoblasts *in vivo* and *in vitro* [45, 52–54], that the stimulation of IGF-I expression coincides with that of runx2 and precedes that of alkaline phosphatase and osteocalcin, that IGF-I directly stimulates osteoblast proliferation and differentiation *in vitro* [13], and that blocking IGF-I action *in vitro* [52] or deleting it [23] or its receptor *in vivo* and *in vitro* blocks the anabolic actions of PTH provide strong evidence that IGF-I is an essential mediator of PTH action.

ROLE OF IGF-I IN MEDIATING THE SKELETAL RESPONSE TO PTH

As previously noted PTH increases the mRNA and protein levels of IGF-I in bone and bone cells both *in vivo* [53, 54] and *in vitro* [52, 55]. IGF-I mRNA and protein are found in highest concentrations in the osteoblasts in the region of bone (primary spongiosa) most responsive to PTH [56]. PTH administration further increases IGF-I mRNA and protein in that region [54]. Continuous PTH has been reported to decrease IGF-I expression compared to intermittent PTH [57], providing one explanation for the observation that continuous PTH has a catabolic rather than anabolic effect on bone. The anabolic action of PTH on bone *in vivo* is blunted in hypophysectomized rats [58] and growth hormone deficient patients [59], but is restored with GH at least in part because of the induction by GH of IGF-I production in bone [60]. IGF-I and its homologous family member IGF-II are both made by bone cells. IGF-I is the dominant IGF in postnatal murine bone, whereas IGF-II dominates in human bone. Although IGF-II has its own receptor, the IGF-IR is the major means by which these growth factors regulate cell growth and differentiation [61].

Liver specific deletion of IGF-I production has minimal impact on skeletal growth [62], but when combined with deletion of the gene for the acid labile subunit to further reduce circulating IGF-I levels, a moderate reduction in bone size and bone mineral density (BMD) is observed [63]. Thus, circulating IGF-I has a role in bone remodeling, but endogenous, *i.e.* skeletal, IGF-I production is likely to play the major role [64, 65].

REGULATION OF IGF ACTION BY IGF-BINDING PROTEINS

Osteoprogenitor cells express all six of the high affinity IGF-binding proteins (IGFBP or BP), and chondrocytes express all but BP-1 [66]. The expression level of these BPs changes with differentiation of the cells [66]. The impact of these BPs on the action of IGF on bone is quite complex, varying according to the BP being evaluated, the molar ratio with IGF, type and differentiation level of cell being evaluated, effect of matrix, posttranscriptional modification, and proteolytic processing [66]. In general all BPs by binding IGF have the potential to inhibit IGF action. However, substantial differences exist among the different BPs. Transgenic overexpression of BP-2 leads to skeletal deficiency [67], but in equimolar concentrations with IGF-II BP-2 can promote rat osteoblast differentiation [68]. This is thought to be due to its binding to the matrix and increasing IGF availability to the osteoblast [69]. The rare syndrome of osteosclerosis in patients with hepatitis C is associated with increased BP-2 [69] perhaps by this mechanism. Transgenic overexpression of BP-3 also leads to a reduction in bone, due to both an increase in osteoclastogenesis and decrease in osteoblast proliferation [70]. However, in combination with equimolar concentrations of IGF-I BP-3/IGF-I increased bone mass in ovariectomized rats [71]. Transgenic overexpression of BP-4 decreased osteoblast number and trabecular bone [72]. However, proteases such as pregnancy associated plasma protein A (PAPP-A) are also expressed in bone and by cleaving BP-4 can release the bound IGF, promoting bone formation [73]. BP-5 is the most abundant BP in both bone and cartilage [66]. Transgenic overexpression of BP-5 results in a gender specific (males more than females) and site specific (periosteal, not endosteal) reduction in bone formation [74, 75], although subcutaneous injection of BP-5 over bone increased trabecular bone formation in ovariectomized mice [76]. This may be

due to the ability of BP-5 to bind to matrix, which decreases its affinity for IGF, and so releasing the IGF in the vicinity of osteoblasts [77]. BPs 1 and 6 have received less study in bone. PTH stimulation of BP-5 expression has been observed [78], but this has not been reported for other BPs.

LESSONS FROM IGF-I TRANSGENIC MICE (TABLE 1)

Mice lacking the ability to produce IGF-I (IGF-IKO) are born small (approx 60% normal weight) and if they survive the birth process fail to grow normally such that by 8 wks of life they are 30% of normal weight [15, 79, 80]. A similar phenotype was found in the one human case reported with an IGF-I deletion [81]. Mice lacking the IGF-IR globally do not survive. Although bone formation is reduced in the IGF-IKO, trabecular bone volume (BV/TV) in the proximal tibia is increased [15], a result reflecting the dual effect of IGF-I on osteoblast and osteoclast activity [14]. Colony forming units are reduced in BMSC cultures from these mice. These mice do not respond to either the anabolic or catabolic actions of PTH [23]. Although the anabolic action of IGF-I is well appreciated, IGF-I, like PTH, is also catabolic. This is indicated by the decrease in BV/TV seen in mice over expressing IGF-I under the control of the collagen IAI promoter [65], although an earlier study in which IGF-I was overexpressed in osteoblasts using an osteocalcin promoter showed an increase in BV/TV at six weeks (but not at 3 or 24 wks) [64]. Furthermore, BV/TV is increased in IGF-IKO [15]. Osteoclasts have IGF-IR [82, 83], may produce IGF-I themselves [56, 84], and IGF-I stimulates RANKL expression and osteoclastogenesis in BMSC [14, 85, 86]. Deleting IGF-IR from osteoclast precursors *in vitro* blocks osteoclastogenesis [14], and in coculture studies these cells block the ability of PTH to stimulate the expression of osteoblast differentiation markers including RANKL. Osteoblasts from IGF-IKO have decreased expression of RANKL and are poor stimulators of osteoclastogenesis [14]. This can be reversed with the addition of IGF-I. Thus, both osteoblasts and osteoclasts are producers and targets of IGF-I, and IGF-I signaling is critical to both the anabolic and catabolic actions of PTH.

To distinguish which cells are responsible for the IGF-IKO phenotype and its lack of responsiveness to PTH, we and others have selectively deleted IGF-I and its receptor from osteoclast precursors and osteoblasts of different maturity. Increased BV/TV and decreased osteoclast numbers were observed when we specifically deleted the IGF-IR from osteoclasts using a TRAP5b driven cre recombinase (IGF-IRocKO) [18]. When the IGF-IR was selectively deleted from mature osteoblasts using an OCN driven cre recombinase (IGF-IRObKO), bone mineralization was reduced, despite normal numbers of osteoblasts [16]. Although the number of colony forming units in BMSC cultures from such mice was normal, the colonies failed to mineralize [30]. In contrast when we deleted IGF-IR from osteoprogenitors using an osterix driven cre recombinase (IGF-IROpKO), osteoblast numbers, proliferation, and differentiation were all reduced resulting in decreased BV/TV [17]. Both IGF-IRObKO and IGF-IROpKO show blunted responses to PTH [7, 17]. In contrast to our studies in which postnatal survival and growth were well maintained in the osteoblast specific knockouts, Govoni *et al.* [87], using a collagen 1 α 2 driven cre recombinase to delete IGF-I from osteoblasts, observed high perinatal mortality and poor growth, with little change in BV/TV in cancellous bone. However, this cre recombinase is not specific for bone, but was found in high levels in muscle and other non skeletal tissues [87].

CONCLUSIONS

Our data are consistent with a major effect of IGF-I signaling in regulating osteoblast proliferation, differentiation, and regulation of osteoclastogenesis. The anabolic and

catabolic actions of PTH are dependent on such signaling. Although the IGF-I receptor plays a critical role in IGF-I signaling, the actual mechanisms by which IGF-I exerts its effects on the various cells of the skeleton remain under active investigation. IGF-I most likely acts in both a paracrine and autocrine fashion, and regulates other cell communication modalities such as RANKL/RANK and EphrinB2/EphB4. Our findings do not discount the importance of other signaling pathways such as wnt, but indicate that one cannot understand the anabolic and catabolic actions of PTH without first considering the role of IGF-I.

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ABBREVIATIONS

AKT	protein kinase B
BFR	bone formation rate
BMD	bone mineral density
BMSC	bone marrow stromal cells
BV/TV	bone volume/tissue volume
c-fms	colony stimulating factor receptor
CREB	cyclic AMP response element binding
C/EBP	ccat element binding protein
Dkk	dickkoff related protein
GH	growth hormone
GSK3β	glycogen synthase kinase 3 beta
IGF	insulin like growth factor
IGF-IR	insulin like growth factor I receptor
IGF-IRKO	deletion of insulin like growth factor I receptor
IGF-IRobKO	deletion of insulin like growth factor I receptor in osteoblasts
IGF-IRocIKO	deletion of insulin like growth factor I receptor in osteoclasts
IGF-IRopKO	deletion of insulin like growth factor I receptor in osteoprogenitors
IGFBP	insulin like growth factor binding protein
IRS	insulin receptor substrate
LRP5	lipoprotein receptor related protein 5
MAPK	mitogen activated protein kinase
m-CSF	macrophage colony stimulating factor
OB	osteoblast
OC	osteoclast
OPG	osteoprotegerin
PI3K	phosphatidyl inositol 3 kinase

PKA	protein kinase A
PTH	parathyroid hormone
PTHr	parathyroid hormone receptor
RANK	receptor activator of NFkB
RANKL	receptor activator of NFkB ligand
SOST	the gene for sclerostin

References

1. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsmann AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001; 344:1434–1441. [PubMed: 11346808]
2. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, Garnero P, Bouxsein ML, Bilezikian JP, Rosen CJ. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med*. 2003; 349:1207–1215. [PubMed: 14500804]
3. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med*. 2003; 349:1216–1226. [PubMed: 14500805]
4. Ma YL, Cain RL, Halladay DL, Yang X, Zeng Q, Miles RR, Chandrasekhar S, Martin TJ, Onyia JE. Catabolic effects of continuous human PTH (1–38) *in vivo* is associated with sustained stimulation of RANKL and inhibition of osteoprotegerin and gene-associated bone formation. *Endocrinology*. 2001; 142:4047–4054. [PubMed: 11517184]
5. Frolik CA, Black EC, Cain RL, Satterwhite JH, Brown-Augsburger PL, Sato M, Hock JM. Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. *Bone*. 2003; 33:372–379. [PubMed: 13678779]
6. Huang JC, Sakata T, Pfeleger LL, Bencsik M, Halloran BP, Bikle DD, Nissenson RA. PTH differentially regulates expression of RANKL and OPG. *J Bone Miner Res*. 2004; 19:235–244. [PubMed: 14969393]
7. Wang Y, Nishida S, Boudignon BM, Burghardt A, Elalieh HZ, Hamilton MM, Majumdar S, Halloran BP, Clemens TL, Bikle DD. IGF-I receptor is required for the anabolic actions of parathyroid hormone on bone. *J Bone Miner Res*. 2007; 22:1329–1337. [PubMed: 17539737]
8. Nishida S, Yamaguchi A, Tanizawa T, Endo N, Mashiba T, Uchiyama Y, Suda T, Yoshiki S, Takahashi HE. Increased bone formation by intermittent parathyroid hormone administration is due to the stimulation of proliferation and differentiation of osteoprogenitor cells in bone marrow. *Bone*. 1994; 15:717–723. [PubMed: 7873302]
9. Wang YH, Liu Y, Buhl K, Rowe DW. Comparison of the action of transient and continuous PTH on primary osteoblast cultures expressing differentiation stage-specific GFP. *J Bone Miner Res*. 2005; 20:5–14. [PubMed: 15619664]
10. Koh AJ, Demiralp B, Neiva KG, Hooten J, Nohutcu RM, Shim H, Datta NS, Taichman RS, McCauley LK. Cells of the osteoclast lineage as mediators of the anabolic actions of parathyroid hormone in bone. *Endocrinology*. 2005; 146:4584–4596. [PubMed: 16081645]
11. Zhao C, Irie N, Takada Y, Shimoda K, Miyamoto T, Nishiwaki T, Suda T, Matsuo K. Bidirectional ephrinB2-EphB4 signaling controls bone homeostasis. *Cell Metab*. 2006; 4:111–121. [PubMed: 16890539]
12. Wang Y, Elalieh H, Chang W, Clemens TL, Bikle D. Ablation of IGF-I signaling disrupts the communication between osteoblasts and osteoclasts. *J Bone Miner Res*. 2007; 22:S241.
13. Kostenuik PJ, Harris J, Halloran BP, Turner RT, Morey-Holton ER, Bikle DD. Skeletal unloading causes resistance of osteoprogenitor cells to parathyroid hormone and to insulin-like growth factor-I. *J Bone Miner Res*. 1999; 14:21–31. [PubMed: 9893062]

14. Wang Y, Nishida S, Elalieh HZ, Long RK, Halloran BP, Bikle DD. Role of IGF-I signaling in regulating osteoclastogenesis. *J Bone Miner Res.* 2006; 21:1350–1358. [PubMed: 16939393]
15. Bikle D, Majumdar S, Laib A, Powell-Braxton L, Rosen C, Beamer W, Nauman E, Leary C, Halloran B. The skeletal structure of insulin-like growth factor I-deficient mice. *J Bone Miner Res.* 2001; 16:2320–2329. [PubMed: 11760848]
16. Zhang M, Xuan S, Boussein ML, von Stechow D, Akeno N, Faugere MC, Malluche H, Zhao G, Rosen CJ, Efstratiadis A, Clemens TL. Osteoblast-specific knockout of the insulin-like growth factor (IGF) receptor gene reveals an essential role of IGF signaling in bone matrix mineralization. *J Biol Chem.* 2002; 277:44005–44012. [PubMed: 12215457]
17. Wang Y, Long R, Elalieh H, Bikle D. Ablation of IGF-I Signaling in Osteoprogenitors Decreases Bone Formation and Blunts the Skeletal Response to PTH. *J Bone Min Res.* 2008; 23:S55.
18. Wang, Y.; Elalieh, H.; Windle, J.; Bikle, D. IGF-I receptor in osteoclast precursors is required for osteoclastogenesis and maintaining normal bone mass. 90th Endocrine Society Annual Meeting; 2008. p. 112
19. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara K. Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. *J Clin Endocrinol Metab.* 2003; 88:4655–4658. [PubMed: 14557436]
20. Miao D, He B, Lanske B, Bai XY, Tong XK, Hendy GN, Goltzman D, Karaplis AC. Skeletal abnormalities in Pth-null mice are influenced by dietary calcium. *Endocrinology.* 2004; 145:2046–2053. [PubMed: 14701672]
21. Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetic K, Muller R, Bilezikian J, Lindsay R. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res.* 2001; 16:1846–1853. [PubMed: 11585349]
22. Misof BM, Roschger P, Cosman F, Kurland ES, Tesch W, Messmer P, Dempster DW, Nieves J, Shane E, Fratzl P, Klaushofer K, Bilezikian J, Lindsay R. Effects of intermittent parathyroid hormone administration on bone mineralization density in iliac crest biopsies from patients with osteoporosis: a paired study before and after treatment. *J Clin Endocrinol Metab.* 2003; 88:1150–1156. [PubMed: 12629098]
23. Bikle DD, Sakata T, Leary C, Elalieh H, Ginzinger D, Rosen CJ, Beamer W, Majumdar S, Halloran BP. Insulin-like growth factor I is required for the anabolic actions of parathyroid hormone on mouse bone. *J Bone Miner Res.* 2002; 17:1570–1578. [PubMed: 12211426]
24. Wang Y, Sakata T, Elalieh HZ, Munson SJ, Burghardt A, Majumdar S, Halloran BP, Bikle DD. Gender differences in the response of CD-1 mouse bone to parathyroid hormone: potential role of IGF-I. *J Endocrinol.* 2006; 189:279–287. [PubMed: 16648295]
25. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R. Anabolic actions of parathyroid hormone on bone. *Endocr Rev.* 1993; 14:690–709. [PubMed: 8119233]
26. Halloran BP, Bikle DD, Harris J, Tanner S, Curren T, Morey-Holton E. Regional responsiveness of the tibia to intermittent administration of parathyroid hormone as affected by skeletal unloading. *J Bone Miner Res.* 1997; 12:1068–1074. [PubMed: 9200006]
27. Iida-Klein A, Zhou H, Lu SS, Levine LR, Ducayen-Knowles M, Dempster DW, Nieves J, Lindsay R. Anabolic action of parathyroid hormone is skeletal site specific at the tissue and cellular levels in mice. *J Bone Miner Res.* 17:808–816. [PubMed: 12009011]
28. Miao D, He B, Karaplis AC, Goltzman D. Parathyroid hormone is essential for normal fetal bone formation. *J Clin Invest.* 2002; 109:1173–1182. [PubMed: 11994406]
29. Goltzman D. Studies on the mechanisms of the skeletal anabolic action of endogenous and exogenous parathyroid hormone. *Arch Biochem Biophys.* 2008; 473:218–224. [PubMed: 18358824]
30. Wang Y, Clemens TL, Bikle DD, Chang W. Chondrocyte-specific knockout of the IGF-IR impedes chondrocyte growth, survival, and differentiation. *J Bone Min Res.* 2006; 21:S50.
31. Rouleau MF, Mitchell J, Goltzman D. *In vivo* distribution of parathyroid hormone receptors in bone: evidence that a predominant osseous target cell is not the mature osteoblast. *Endocrinology.* 1988; 123:187–191. [PubMed: 2838253]

32. Lee K, Deeds JD, Chiba S, Un-No M, Bond AT, Segre GV. Parathyroid hormone induces sequential c-fos expression in bone cells *in vivo*: in situ localization of its receptor and c-fos messenger ribonucleic acids. *Endocrinology*. 1994; 134:441–450. [PubMed: 8275957]
33. Irie K, Ozawa H. Immunohistochemical localization of parathyroid hormone/parathyroid hormone-related peptide receptor in rat tibiae. *J Bone Miner Metab*. 1996; 14:10–14.
34. Dempster DW, Hughes-Begos CE, Plavetic-Chee K, Brandao-Burch A, Cosman F, Nieves J, Neubort S, Lu SS, Iida-Klein A, Arnett T, Lindsay R. Normal human osteoclasts formed from peripheral blood monocytes express PTH type 1 receptors and are stimulated by PTH in the absence of osteoblasts. *J Cell Biochem*. 2005; 95:139–148. [PubMed: 15723294]
35. Merciris D, Marty C, Collet C, de Vernejoul MC, Geoffroy V. Overexpression of the transcriptional factor Runx2 in osteoblasts abolishes the anabolic effect of parathyroid hormone *in vivo*. *Am J Pathol*. 2007; 170:1676–1685. [PubMed: 17456773]
36. Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. *Bone*. 2007; 40:1434–1446. [PubMed: 17517365]
37. Onyia JE, Bidwell J, Herring J, Hulman J, Hock JM. *In vivo*, human parathyroid hormone fragment (hPTH 1-34) transiently stimulates immediate early response gene expression, but not proliferation, in trabecular bone cells of young rats. *Bone*. 1995; 17:479–484. [PubMed: 8579960]
38. Swarthout JT, D'Alonzo RC, Selvamurugan N, Partridge NC. Parathyroid hormone-dependent signaling pathways regulating genes in bone cells. *Gene*. 2002; 282:1–17. [PubMed: 11814673]
39. Clohisy JC, Scott DK, Brakenhoff KD, Quinn CO, Partridge NC. Parathyroid hormone induces c-fos and c-jun messenger RNA in rat osteoblastic cells. *Mol Endocrinol*. 1992; 6:1834–1842. [PubMed: 1480173]
40. Onishi T, Zhang W, Cao X, Hruska K. The mitogenic effect of parathyroid hormone is associated with E2F-dependent activation of cyclin-dependent kinase 1 (cdc2) in osteoblast precursors. *J Bone Miner Res*. 1997; 12:1596–1605. [PubMed: 9333120]
41. Wang YH, Liu Y, Rowe DW. Effects of transient PTH on early proliferation, apoptosis, and subsequent differentiation of osteoblast in primary osteoblast cultures. *Am J Physiol Endocrinol Metab*. 292:E594–603. [PubMed: 17032929]
42. Samadfam R, Xia Q, Goltzman D. Co-treatment of PTH with osteoprotegerin or alendronate increases its anabolic effect on the skeleton of oophorectomized mice. *J Bone Miner Res*. 2007; 22:55–63. [PubMed: 17014384]
43. Allan EH, Hausler KD, Wei T, Gooi JH, Quinn JM, Crimeen-Irwin B, Pompolo S, Sims NA, Gillespie MT, Onyia JE, Martin TJ. EphrinB2 Regulation by Parathyroid Hormone (PTH) and PTHrP Revealed by Molecular Profiling in Differentiating Osteoblasts. *J Bone Miner Res*. 2008; 23:1170–1181. [PubMed: 18627264]
44. Lee SK, Lorenzo JA. Parathyroid hormone stimulates TRANCE and inhibits osteoprotegerin messenger ribonucleic acid expression in murine bone marrow cultures: correlation with osteoclast-like cell formation. *Endocrinology*. 1999; 140:3552–3561. [PubMed: 10433211]
45. Centrella M, Christakos S, McCarthy TL. Skeletal hormones and the C/EBP and Runx transcription factors: interactions that integrate and redefine gene expression. *Gene*. 2004; 342:13–24. [PubMed: 15527960]
46. Yang D, Singh R, Divieti P, Guo J, Boussein ML, Bringham FR. Contributions of parathyroid hormone (PTH)/PTH-related peptide receptor signaling pathways to the anabolic effect of PTH on bone. *Bone*. 2007; 40:1453–1461. [PubMed: 17376756]
47. Kulkarni NH, Halladay DL, Miles RR, Gilbert LM, Frolik CA, Galvin RJ, Martin TJ, Gillespie MT, Onyia JE. Effects of parathyroid hormone on Wnt signaling pathway in bone. *J Cell Biochem*. 2005; 95:1178–1190. [PubMed: 15962290]
48. Suzuki A, Ozono K, Kubota T, Kondou H, Tachikawa K, Michigami T. PTH/cAMP/PKA signaling facilitates canonical Wnt signaling *via* inactivation of glycogen synthase kinase-3 β in osteoblastic Saos-2 cells. *J Cell Biochem*. 104:304–317. [PubMed: 17990294]
49. Keller H, Kneissel M. SOST is a target gene for PTH in bone. *Bone*. 2005; 37:148–158. [PubMed: 15946907]
50. Sawakami K, Robling AG, Ai M, Pitner ND, Liu D, Warden SJ, Li J, Maye P, Rowe DW, Duncan RL, Warman ML, Turner CH. The Wnt co-receptor LRP5 is essential for skeletal

- mechanotransduction but not for the anabolic bone response to parathyroid hormone treatment. *J Biol Chem.* 2006; 281:23698–23711. [PubMed: 16790443]
51. Iwaniec UT, Wronski TJ, Liu J, Rivera MF, Arzaga RR, Hansen G, Brommage R. PTH stimulates bone formation in mice deficient in Lrp5. *J Bone Miner Res.* 2007; 22:394–402. [PubMed: 17147489]
 52. Canalis E, Centrella M, Burch W, McCarthy TL. Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. *J Clin Invest.* 1989; 83:60–65. [PubMed: 2910920]
 53. Pfeilschifter J, Laukhuf F, Muller-Beckmann B, Blum WF, Pfister T, Ziegler R. Parathyroid hormone increases the concentration of insulin-like growth factor-I and transforming growth factor beta 1 in rat bone. *J Clin Invest.* 1995; 96:767–774. [PubMed: 7635970]
 54. Watson P, Lazowski D, Han V, Fraher L, Steer B, Hodsman A. Parathyroid hormone restores bone mass and enhances osteoblast insulin-like growth factor I gene expression in ovariectomized rats. *Bone.* 1995; 16:357–365. [PubMed: 7786639]
 55. Linkhart TA, Mohan S. Parathyroid hormone stimulates release of insulin-like growth factor-I (IGF-I) and IGF-II from neonatal mouse calvaria in organ culture. *Endocrinology.* 1989; 125:1484–1491. [PubMed: 2759029]
 56. Lazowski DA, Fraher LJ, Hodsman A, Steer B, Modrowski D, Han VK. Regional variation of insulin-like growth factor-I gene expression in mature rat bone and cartilage. *Bone.* 1994; 15:563–576. [PubMed: 7980968]
 57. Locklin RM, Khosla S, Turner RT, Riggs BL. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. *J Cell Biochem.* 2003; 89:180–190. [PubMed: 12682918]
 58. Hock JM, Canalis E, Centrella M. Transforming growth factor-beta stimulates bone matrix apposition and bone cell replication in cultured fetal rat calvariae. *Endocrinology.* 1990; 126:421–426. [PubMed: 2293996]
 59. White HD, Ahmad AM, Durham BH, Patwala A, Whittingham P, Fraser WD, Vora JP. Growth hormone replacement is important for the restoration of parathyroid hormone sensitivity and improvement in bone metabolism in older adult growth hormone-deficient patients. *J Clin Endocrinol Metab.* 2005; 90:3371–3380. [PubMed: 15741264]
 60. LeRoith D, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis: 2001. *Endocr Rev.* 2001; 22:53–74. [PubMed: 11159816]
 61. LeRoith D, Werner H, Beitner-Johnson D, Roberts CT Jr. Molecular and cellular aspects of the insulin-like growth factor I receptor. *Endocr Rev.* 1995; 16:143–163. [PubMed: 7540132]
 62. Yakar S, Liu JL, Stannard B, Butler A, Accili D, Sauer B, LeRoith D. Normal growth and development in the absence of hepatic insulin-like growth factor I. *Proc Natl Acad Sci USA.* 1999; 96:7324–7329. [PubMed: 10377413]
 63. Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu JL, Ooi GT, Setser J, Frystyk J, Boisclair YR, LeRoith D. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest.* 2002; 110:771–781. [PubMed: 12235108]
 64. Zhao G, Monier-Faugere MC, Langub MC, Geng Z, Nakayama T, Pike JW, Chernauek SD, Rosen CJ, Donahue LR, Malluche HH, Fagin JA, Clemens TL. Targeted overexpression of insulin-like growth factor I to osteoblasts of transgenic mice: increased trabecular bone volume without increased osteoblast proliferation. *Endocrinology.* 2000; 141:2674–2682. [PubMed: 10875273]
 65. Clemens TL, Chernauek SD. Genetic strategies for elucidating insulin-like growth factor action in bone. *Growth Horm IGF Res.* 2004; 14:195–199. [PubMed: 15125880]
 66. Hoeflich A, Gotz W, Lichanska AM, Bielohuby M, Tonshoff B, Kiepe D. Effects of insulin-like growth factor binding proteins in bone -- a matter of cell and site. *Arch Physiol Biochem.* 2007; 113:142–153. [PubMed: 17922310]
 67. Eckstein F, Pavicic T, Nedbal S, Schmidt C, Wehr U, Rambeck W, Wolf E, Hoeflich A. Insulin-like growth factor-binding protein-2 (IGFBP-2) overexpression negatively regulates bone size and mass, but not density, in the absence and presence of growth hormone/IGF-I excess in transgenic mice. *Anat Embryol.* 2002; 206:139–148. [PubMed: 12478375]

68. Palermo C, Manduca P, Gazzero E, Foppiani L, Segat D, Barreca A. Potentiating role of IGFBP-2 on IGF-II-stimulated alkaline phosphatase activity in differentiating osteoblasts. *Am J Physiol Endocrinol Metab.* 2004; 286:E648–657. [PubMed: 14665441]
69. Khosla S, Hassounm AA, Baker BK, Liu F, Zein NN, Whyte MP, Reasner CA, Nippoldt TB, Tiegs RD, Hintz RL, Conover CA. Insulin-like growth factor system abnormalities in hepatitis C-associated osteosclerosis. Potential insights into increasing bone mass in adults. *J Clin Invest.* 1998; 101:2165–2173. [PubMed: 9593772]
70. Silha JV, Mishra S, Rosen CJ, Beamer WG, Turner RT, Powell DR, Murphy LJ. Perturbations in bone formation and resorption in insulin-like growth factor binding protein-3 transgenic mice. *J Bone Miner Res.* 2003; 18:1834–1841. [PubMed: 14584894]
71. Bagi CM, DeLeon E, Brommage R, Rosen D, Sommer A. Treatment of ovariectomized rats with the complex of rhIGF-I/IGFBP-3 increases cortical and cancellous bone mass and improves structure in the femoral neck. *Calcif Tissue Int.* 57:40–46. [PubMed: 7545533]
72. Zhang M, Faugere MC, Malluche H, Rosen CJ, Chernauek SD, Clemens TL. Paracrine overexpression of IGFBP-4 in osteoblasts of transgenic mice decreases bone turnover and causes global growth retardation. *J Bone Miner Res.* 2003; 18:836–843. [PubMed: 12733722]
73. Qin X, Wergedal JE, Rehage M, Tran K, Newton J, Lam P, Baylink DJ, Mohan S. Pregnancy-associated plasma protein-A increases osteoblast proliferation *in vitro* and bone formation *in vivo*. *Endocrinology.* 2006; 147:5653–5661. [PubMed: 16946002]
74. Devlin RD, Du Z, Buccilli V, Jorgetti V, Canalis E. Transgenic mice overexpressing insulin-like growth factor binding protein-5 display transiently decreased osteoblastic function and osteopenia. *Endocrinology.* 2002; 143:3955–3962. [PubMed: 12239107]
75. Salih DA, Mohan S, Kasukawa Y, Tripathi G, Lovett FA, Anderson NF, Carter EJ, Wergedal JE, Baylink DJ, Pell JM. Insulin-like growth factor-binding protein-5 induces a gender-related decrease in bone mineral density in transgenic mice. *Endocrinology.* 2005; 146:931–940. [PubMed: 15550514]
76. Andress DL. IGF-binding protein-5 stimulates osteoblast activity and bone accretion in ovariectomized mice. *Am J Physiol Endocrinol Metab.* 2001; 281:E283–288. [PubMed: 11440904]
77. Mohan S, Nakao Y, Honda Y, Landale E, Leser U, Dony C, Lang K, Baylink DJ. Studies on the mechanisms by which insulin-like growth factor (IGF) binding protein-4 (IGFBP-4) and IGFBP-5 modulate IGF actions in bone cells. *J Biol Chem.* 1995; 270:20424–20431. [PubMed: 7544787]
78. Erlik MS, Mitchell J. Activation of the insulin-like growth factor binding protein-5 promoter by parathyroid hormone in osteosarcoma cells requires activation of an activated protein-2 element. *J Mol Endocrinol.* 2005; 34:713–722. [PubMed: 15956342]
79. Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A. Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) type, 1 IGF receptor (Igf1r). *Cell.* 1993; 75:59–72. [PubMed: 8402901]
80. Baker J, Liu JP, Robertson EJ, Efstratiadis A. Role of insulin-like growth factors in embryonic and postnatal growth. *Cell.* 1993; 75:73–82. [PubMed: 8402902]
81. Camacho-Hubner C, Woods KA, Clark AJ, Savage MO. Insulin-like growth factor (IGF)-I gene deletion. *Rev Endocr Metab Disord.* 2002; 3:357–361. [PubMed: 12424437]
82. Hou P, Sato T, Hofstetter W, Foged NT. Identification and characterization of the insulin-like growth factor I receptor in mature rabbit osteoclasts. *J Bone Miner Res.* 12:534–540. [PubMed: 9101364]
83. Fiorelli G, Formigli L, Zecchi Orlandini S, Gori F, Falchetti A, Morelli A, Tanini A, Benvenuti S, Brandi ML. Characterization and function of the receptor for IGF-I in human preosteoclastic cells. *Bone.* 1996; 18:269–276. [PubMed: 8703583]
84. Hayden JM, Mohan S, Baylink DJ. The insulin-like growth factor system and the coupling of formation to resorption. *Bone.* 1995; 17:93S–98S. [PubMed: 8579905]
85. Hill PA, Reynolds JJ, Meikle MC. Osteoblasts mediate insulin-like growth factor-I and -II stimulation of osteoclast formation and function. *Endocrinology.* 1995; 136:124–131. [PubMed: 7828521]

86. Rubin J, Ackert-Bicknell CL, Zhu L, Fan X, Murphy TC, Nanes MS, Marcus R, Holloway L, Beamer WG, Rosen CJ. IGF-I regulates osteoprotegerin (OPG) and receptor activator of nuclear factor-kappaB ligand *in vitro* and OPG *in vivo*. J Clin Endocrinol Metab. 2002; 87:4273–4279. [PubMed: 12213884]
87. Govoni KE, Wergedal JE, Florin L, Angel P, Baylink DJ, Mohan S. Conditional deletion of insulin-like growth factor-I in collagen type 1alpha2-expressing cells results in postnatal lethality and a dramatic reduction in bone accretion. Endocrinology. 2007; 148:5706–5715. [PubMed: 17717052]

Fig. 1. The role of IGF-I in the anabolic and catabolic actions of PTH: working model

PTH stimulates IGF-I production in osteoblasts through a cAMP dependent mechanism. The IGF-I so produced enhances the proliferation and differentiation of osteoprogenitors, at least in part by activating both the MAPK and PI3K pathways, and enables the expression of both RANKL and m-CSF which along with IGF-I promote the differentiation of osteoclasts. The osteoclasts in turn facilitate osteoblast differentiation *via* Ephrin B2:EphB4 signaling, the expression of which is also dependent on IGF-I.

Table 1

Deletion models of IGF and IGF-IR and their Influence on PTH action.

Model	Impact on bone	Effect on PTH actions	reference
Global IGF-IKO	↓ BFR ↑ BV/TV ↓ Ocl	Blocks effect on BFR	[23]
Osteoblast specific IGF-IR KO	↓ Mineralization normal OB	Blocks effect on osteoprogenitor proliferation and differentiation	[7, 16]
Osteoprogenitor specific IGF-IR KO	↓ OB ↓ BV/TV ↓ Mineralization ↓ Differentiation	Blocks stimulation of RANKL and ephrin b2 expression	[17]
Osteoclast specific IGF-IR KO	↓ Ocl ↑ BV/TV	ND	[14, 18]

BFR: bone formation rate; BV/TV = bone volume/total volume; Ocl = osteoclast; OB = osteoblast; ND = not done.